UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/982,284	12/01/97	LUBON H	030523/0141

HM12/1117

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON DC 20007-5109

EXAMINER	
WILSON,M	
ART UNIT	**PAPER NUMBER**
1633	19

DATE MAILED: 11/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/982,284	Applicant(s) Lubon et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *5-7, 11-13, 15, 45-47, 51-57, 61-65, and 67-74* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *5-7, 11-13, 15, 45-47, 51-57, 61-65, and 67-74* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The following is a supplemental office action that supercedes the previous office action mailed 6-5-00. Applicant's amendment was filed February 29, 2000, paper number 16. Claims 1, 8, 16-44, 48-50, 58-60 and 66 were canceled. Claims 67-71 were added. Claims 5-7, 11-13, 15, 45-47, 51-57, 61-65 and 67-74 are pending.

PTO-1449 Consideration

The Examiner has considered the translated abstract of FR 2 717 500 and Velander, W., July, 1997 as requested by applicants.

Sequence Compliance

The prior objection to the specification with respect to sequence compliance is withdrawn in view of applicants submission of an effective sequence listing.

Claim Objections

Claim 63, as amended, is objected to as depending from claim 56 and 72 without indicating that these are in the alternative.

Claim Rejections - 35 USC § 112

Claims 5-7, 11-13, 15, 45-47, 51-57, and 61-65 stand rejected and claims 67-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate with the scope of the claimed invention.

While the specification is enabled for a **non-human transgenic mammal** whose genome comprises an nucleic acid sequence comprising a whey acidic promoter (WAP) operably linked to a gene encoding a modified stromelysin-1 gene as taught by the prior art, wherein expression of said stromelysin-1 gene by somatic cells in said transgenic mammal results in the production of said protein in the urine of said transgenic mammal; and methods of producing the same or other transgenic mice known in the art to secrete a protein which detoxifies or degrades organic material in the urine. The specification does not reasonably provide enablement for the breadth of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue that there is no undue experimentation to produce transgenic animals of any and all species given that the specification supports that Protein C was produced in both transgenic mice and pigs. However, as discussed in the previous office action, the examples provided in Figure 5 and Table III are limited to the production of transgenic mammals using the WAP promoter. The prior art has demonstrated that mammary specific regulatory regions can reproducibly direct a protein of interest to the milk, blood, or urine of a representative number of transgenic **mammals** (see USPN 5,880,327, for example). However, this is the exception to the unpredictable transgenic art and has not been found to be the norm as is supported by the teachings of Strojek and Wagner, Houdebine, Wall and Kappel as set forth in the previous office action. In fact, some of applicants claims encompass the production of transgenic dogs, cats, and

horses, but to date none of these mammals have been transgenically produced using any transgene construct. Furthermore, the methods of producing transgenic birds and reptiles differs dramatically from that of transgenic mammals and there is no evidence that mammalian promoters would function in these species or that correlative regulatory sequences even exist or could be identified in these species.

It is further noted that applicants have limited their claims to proteins with degrade or detoxify organic material, however, there is no evidence within the specification or the prior art that protein C can detoxify or degrade organic material. Organic material encompasses connective tissues and organs which are essential to the generation of a transgenic animal, however, applicants specification fails to teach how toxic proteins and peptides can be altered to generate transgenic animals without degrading the tissues of the animal. D'Armiento et al. teach the production of a matrix matalloproteinase (MMP) collagenase transgenic mouse to study the expression of the human collagenase in the epithelium of the tissue (page 5734, column 2, line 6; also see the abstract). These mice die shortly after birth. MMP's are a class of extracellular matirix degrading enzymes which are clearly encompassed within the phrase "degrades or detoxifies organic material." Therefore, it is evident that the expression of proteins that degrade or detoxify organic material may have an effect on the growing organs or tissues such that survival of the animal is unpredictable. Applicant's claims are directed to any and all proteins or peptides which degrade or detoxify organic material, yet the specification fails to teach one of skill in the art how to identify appropriate proteins or peptides which can be used to generate

transgenic animals such that the animals survive and produce the protein in the urine to measurable amounts. In fact, the specification fails to provide a working example for a single transgenic animal expressing a protein or peptide which degrades or detoxifies organic material, yet the claimed are directed to all transgenic animals expressing any or all proteins or peptides which degrade or detoxify organic material.

Applicant's argue that prior to the effective filing date many researchers were producing many different proteins in a "broad range of hosts." The Examiner does not contradict this. However, the prior art clearly teaches that the particular transgene construct is imperative to the ability to produce a transgenic animal with a predictable phenotype. The level and the specificity of expression of a transgene as well as the phenotype of the transgenic animal thus produced are greatly dependent of the **specific** transgene construct used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are all important factors in controlling the expression of a transgene. Applicant's specification in conjunction with the prior art only supports the production of proteins in the urine with transgene constructs utilizing the WAP promoter for mammals and the uroplakin II promoter in mice operably linked to a protein which **does not** degrade or detoxify organic material. The specification fails to teach one of skill in the art how to utilize these promoters with genes known in the art to degrade or detoxify organic material such that a transgenic mouse or pig could be produced and survive to produce a protein which degrades or detoxifies organic material in the urine of the mammal. While the prior art does teach expression of a modified

stromelysin-1 enzyme under control of the WAP promoter (see Sympson et al. below), the specification fails to teach how to modify the numerously claimed enzymes listed in Figure 7, or other enzymes encompassed by the claims, such that viable transgenic animals can be produced. Nor does the specification teach any 5' or 3' "urinary tract-specific regulatory sequences" (claims 67-74. While sequences may provide expression in urinary tract tissue such as kidney, it is not readily apparent that any regulatory element is specific to all tissue in the urinary tract or to even to a particular tissue of the urinary tract such as the kidney. In addition, it is not readily apparent that the promoter must be specific to the urinary tract because it may also be expressed elsewhere, e.g. the WAP promoter provides expression in mammary and kidney tissue. Finally, the specification does not teach any 3' urinary-tract-specific regulatory sequence that functions to target protein expression to the urinary tract or that is specific to all urinary-tract tissue. Therefore, the claimed invention is enabling only for a **non-human transgenic mammal** whose genome comprises an nucleic acid sequence comprising a whey acidic promoter (WAP) operably linked to a gene encoding a modified stromelysin-1 gene as taught by the prior art, wherein expression of said stromelysin-1 gene by somatic cells in said transgenic mammal results in the production of said protein in the urine of said transgenic mammal; and methods of producing the same or other transgenic mice known in the art to secrete a protein which detoxifies or degrades organic material in the urine.

Therefore, for the reasons set forth above and in the previous office action, the rejection is maintained.

The prior rejection of claims 52, 53, 62, and 63 under 35 USC § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

The prior rejection of claims 1, 5-8, 11-13, 15 and 45-65 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Claim Rejections - 35 USC § 102

The prior rejection of claims 45-49, 51, 52, 54-59, 61, 62, 64 and 65 under 35 U.S.C. 102(b) as being anticipated by Sun et al (USPN 5,824,543). or Sun et al.(WO 96/39494) is withdrawn.

The prior rejection of claims 45-49, 51, 52, 54-59, 61, 62, 64 and 65 under 35 U.S.C. 102(b) as being anticipated by Lubon et al. is withdrawn.

Claims 56-57, 61, 64, 65 and 71-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Sympson et al.

Sympson et al. taught the production of a transgenic mouse expressing a rat stromelysin-1 cDNA under control of the WAP promoter. The WAP promoter directs expression inherently

into the kidney and results in protein production in the urine (see page 28, line 24 of the specification or USPN 5,880,327, column 6). The WAP promoter is equivalent to a 5' urinary tract-specific regulatory sequence. Therefore, Sympson et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The prior rejection of claims 1, 5-8, 11-13, 15, 45-52, 54-62, 64 and 65 under 35 U.S.C. 103(a) as being unpatentable over Sun et al.(USPN 5,824,543). or Sun et al.(WO 96/39494) in view of Lubon et al. is withdrawn.

Claims 45-47, 51, 54, 55 and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sympson et al. in view of Wen et al. (PTO-1449, A41) and Lubon et al. (USPN 5,880,327).

Sympson et al. taught the production of a transgenic mouse expressing a rat stromelysin-1 cDNA under control of the WAP promoter. The WAP promoter directs expression inherently in the kidney resulting in protein production in the urine (see page 28, line 24 of the specification or USPN 5,880,327, column 6). Sympson et al. does not suggest that the stromelysin-1 gene could be isolated from the urine. However, at the time the claimed invention was made, Wen et al. and Lubon et al. taught that proteins of interest could be isolated from other tissues, such as the urine, using the WAP promoter. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to collect and isolate stromelysin-1 protein from the urine

of the transgenic mice produced by Sympson et al. with a reasonable expectation of success. Therefore, the claimed invention was *prima facie* obvious in the absence of evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Michael C. Wilson

Karen M. Hauda

KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600